CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

Metalaxyl

Chemical Code # 002132, Tolerance # 00408
SB 950 # 198

Original date
Revised date: 2/15/96

I. DATA GAP STATUS

Chronic toxicity, rat:	No data gap, no adverse effect
Chronic toxicity, dog:	No data gap, no adverse effect
Oncogenicity, rat:	No data gap, possible adverse effect
Oncogenicity, mouse:	No dat gap, no adverse effect
Reproduction, rat:	No data gap, no adverse effect
Teratology, rat:	No data gap, no adverse effect
Teratology, rabbit:	No data gap, no adverse effect
Gene mutation:	No data gap, no adverse effect

Chromosome effects:	No data gap, possible adverse effect
DNA damage:	No data gap, no adverse effect
Neurotoxicity:	Not required at this time

Toxicology one-liners are attached.

All record numbers through 115268 and 990440 were examined.
** indicates an acceptable study.
Bold face indicates a possible adverse effect.

File name: T960215
Prepared by H. Green, 12/18/95, and P. Iyer, 2/2/96 [and J. Gee, 2/15/96].

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

U. S. EPA produced at reregistration document entitled "Reregistration Eligibility Decision (RED): Metalaxyl", dated September 1994.

COMBINED, RAT

** 006, 007, 008, 064, 065, 066 990425, 990426, 990427, 990429, 990430, 990422 "CGA 48 988: Toxicity and Oncogenicity in Dietary Administration to Rats for Two Years", (R. Ashby, Life Science Research, England, Report # 80/CIA009/315, 23 September 1980). The test article is identified as CGA 48 988 (metalaxyl) with 93% purity. 80 CD (Sprague-Dawley derived) rats per sex per group received 0, 50, 250, and 1250 ppm in the diet for 105 weeks. 10 per sex per group were necropsied after 55 weeks of treatment. Group mean liver weights relative to bodyweights were increased for high dose females at 55 week sacrifice and for mid and high dose males and high dose females at the 105 week sacrifice. Also in females at 105 weeks an increase in the incidence of follicular cell adenomas of the thyroid were noted at 50, 250 and 1250 ppm. Chronic NOEL = 50 ppm. Oncogenicity NOEL = 1250 ppm. Originally reviewed as acceptable (J. Remsen, 5/29/85). Re-reviewed as **acceptable** (H. Green and Gee, 2/14/96).

408-003 990419 "3 months dietary study in rats with compound CGA 48 988: (J. C. Drake, Geigy Pharmaceuticals, 2/25/77) CGA 48 988 technical, 99%, batch P.3, was fed in the diet to Sprague Dawley rats for 3 months. There were 25/sex fed 0 or 1250 ppm and 20/sex fed at 50 or 250 ppm. Five per sex in the control and 1250 ppm groups were held for 1 month recovery period following treatment. Observations included hematology, limited clinical chemistry, urinalysis and clinical observations with no treatment-related affects identified. There was a slight increase in liver weights in the treated groups. The only affect of note was minimal hypertrophy in some female rats at 1250 ppm, considered by the author to be "physiological ’work’ hypertrophy". Supplemental for dose setting for the 2-year study. (Gee, 2/9/96).

CHRONIC, DOG

** 010, 255 990417, 115268, "Six Month Chronic Oral Toxicity Study with CGA-48988 Technical in Beagle Dogs", (L. Steven Beck, D.V.M., M.S., Elars Bioresearch Laboratories, Inc., Fort Collins, CO., Project # 1545, 20 January 1981). The test article is identified as CGA-48988 (metalaxyl) technical with 92% purity. 6 or 8 (control and high dose) Beagle dogs per sex per group received 0, 50, 250, and 1000 ppm in the diet for 180 days. 2 per sex from the control and high dose groups served as recovery animals and were fed untreated diet for an additional 4 weeks. Variations in hematology and serum chemistry parameters (increase in alkaline phosphatase levels) fall within historical control ranges. Chronic NOEL = 50 ppm (Group mean liver weights relative to brain weight were increased at the mid and high dose levels). Histopathology revealed no remarkable changes. NOAEL = 1000 ppm. **Study design does not meet with current guidelines.** However, since no adverse changes other than hepatomegaly were noted at a nominal 1000 ppm the study previously reviewed as unacceptable, upgradeable upon submission of dietary concentration is now acceptable. (H. Green, and P. Iyer, 1/31/96).

ONCOGENICITY, RAT

103 024214, "Carcinogenicity of the Fungicide Ridomil* 25WP in Albino Rats", (R. Fytizas and G. Vassiliou, Institution of Phytopathology Benaki, Athens, Greece). The test article is identified as Ridomil* WP 25. 15 (treated) or 20 (control) Wistar-derived rats per sex per group received 0, 200, 400, and 800 mg/kg in the diet for 23 months. **Lymphoma is indicated**. Insufficient information for NOEL determination. **Unacceptable** and not upgradeable (dosing level rationale, incomplete results presentation, etc.). (J. Remsen, 5/28/85; updated to electronic format, H. Green, 10/18/95).

ONCOGENICITY, MOUSE

** 045, 112, 254, 256, 257 036174, 115267, 115269, 115270, "CGA 48988: Oncogenicity in Dietary Administration to Mice for Two Years, Final Report", (T.W. McSheehy, Life Science Research, England, Report # 80/CIA008/442, 31 October 1980). The test article is identified as CGA 48988 (metalaxyl, 93.8% - 95.2% purity). 60 ICI Alderley Park (Swiss strain origin) mice per sex per group received 0, 50, 250, and 1250 ppm of test article in the diet for 104 weeks. Large hepatocytic fatty vacuolation was increased for high dose males and females killed and dying during weeks 0 to 104 and for high dose males at terminal sacrifice compared to controls. Bodyweights for high dose males were reduced 5% to 10% during treatment weeks 22 through 90. Chronic NOEL = 250 ppm (liver changes and reduced bodyweights in high dose males). Oncogenicity NOEL = 1250 ppm. NOAEL = 1250 ppm. Unacceptable but upgradeable upon submission of rationale for dosing and test article characterization (J. Remsen, 5/30/85 (Record # 036174 only); reviewed after submission of rationale for dosing and purity of test material. **Acceptable** (H. Green and Gee, 2/23/96).

REPRODUCTION, RAT

009 990432, "Effect of CGA 48-988 on Reproductive Function of Multiple Generations in the Rat", (David D. Cozens, *et. al.*, Huntingdon Research Centre, Huntingdon, Cambridgeshire, England, Report # CBG 181/80254, 23 May 1980). The test article is identified as CGA 48-988 (metalaxyl) technical with 93.5% purity. 12 to 25 Crl:COBS CD (SD) BR strain rats per sex per group received 0, 50, 250, and 1250 ppm in the diet through 3 generations with 2 litters per generation. Decreased bodyweights were noted for F1 parental males and females and for F2 males at the mid and high dose levels. Parental NOEL = 50 ppm. Reproductive NOEL = 1250 ppm. NOAEL = 1250 ppm. **Acceptable.
(J. Remsen, 5/30/85; updated to electronic format, H. Green, 10/2/95).

TERATOLOGY, RAT

003 990431, "Reproduction Study, CGA 48988 tech., Rat Seg. II (Test for Teratogenic or Embryotoxic Effects)", (Dr. H. Fritz, Ciba-Geigy Limited, Pharmaceuticals Division, Toxicology/Pathology, Basle, Switzerland, Report # 227716, 7 February 1978). The test article is identified as CGA 48988 (metalaxyl) technical. 25 mated Sprague-Dawley derived (Tif/RAI) female rats per group received 0, 20, 60, and 120 mg/kg/day on gestation days 6 through 15. **Teratogenicity is not indicated**. Previously reviewed as Unacceptable and

not upgradeable (dosing level rationale, incomplete results, dosing characterization). (J. Remsen, 5/28/85; updated to electronic format, H. Green, 10/26/95).

** 115 036187, 254 115257 "Teratology Study in Rats", (James L. Schardein, M.S., International Research and Development Corporation, Report # 382-100, 3 January 1985). The test article is identified as metalaxyl technical. 27 or 38 (high dose group) mated Charles River COBS* CD* female rats received 0, 50, 250, and 400 mg/kg/day by gavage on gestation days 6 through 15. At 400 mg/kg/day, all dams had convulsions after dosing and 12 of 38 died. At 250 mg/kg/day, 1 of 27 died and 10 had convulsions after dosing. Maternal NOEL = 50 mg/kg/day. Developmental NOEL = 400 mg/kg/day. **Unacceptable** and upgradeable (dosing suspension analyses, dosing rationale). (J.Parker, 11/18/85). Upgraded to Acceptable upon submission of analysis of dosing suspension in 254 115257 (P. Iyer, 1/31/96).

254 115257, "Teratology Study in Rats", Supplemental Information submitted in response to data call-in. (Ciba-Geigy Corporation, Ag. Division, N.C. 6/2/92).
Analyses of dosing suspensions used in previously submitted teratology studies 115 036186 and 036187. Analysis of dosing suspensions prepared prior to initiation and administration in the first week of the study (036186) demonstrated levels of Metalaxyl between 91 and 104% of target concentrations. Test material was determined to be stable in suspension for 6 hours in pilot study. The rationale for dosage selection in 036187 from the results of the range-finding study (036186) remains unclear. The analysis of dosing suspension and along with submission of methods used for the analyses upgrades the study to Acceptable (P. Iyer 1/31/96).

115 036186 "Range-finding teratology study in rats." (James L. Schardein, International Research and Development Corporation, Report # 382-099, 1/3/85) Five mated Charles River COBS CD female rats per group received metalaxyl technical at 0 (1% methylcellulose), 75, 125, 250 or 500 mg/kg/day by gavage on gestation days 6 through 15. All dams survived. Clinical signs at 500 mg/kg/day included decreased activity, unsteadiness, stained abdominal haircoat, lacrimation. A slight inhibition in food consumption and bodyweight gain were seen at 250 and 500 mg/kg/day. No changes in Cesarean section parameters were reported. No separate worksheet. (Green and Iyer, 1/31/96)

TERATOLOGY, RABBIT

** 114 036184, 036185, 254 115256 "Teratology Study in Rabbits", (Michael F. Kenel, Ph.D., International Research and Development Corporation, Report # 382-098, 4 December 1984). The test article is identified as metalaxyl technical. 18 inseminated Dutch Belted female rabbits per group received 0 (1% methylcellulose), 30, 150, and 300 mg/kg/day by gavage on gestation days 7 through 19. Bodyweight gain and food consumption were reduced for high dose dams during the treatment period. Maternal NOEL = 150 mg/kg/day. Developmental NOEL = 300 mg/kg/day. Previously reviewed to be Unacceptable, upgradeable upon submission of analysis of test material (V. de Vlaming and J. Parker, 11/20/85). 254 115256 provided analysis of dosing material suspensions, upgraded to Acceptable (P. Iyer, 1/29/96).

GENE MUTATION

003 990438, "Salmonella/Mammalian-Microsome Mutagenicity Test with CGA 48988 (Test for Mutagenic Properties in Bacteria)", (Dr. P. Arni and Prof. Dr. D. Muller, Ciba-Geigy Limited, Pharmaceuticals Division, Toxicology/Pathology, Basle, Switzerland, Report # 78-2514, 14 March 1978). The test article is identified as CGA 48988 (metalaxyl, batch P2). Salmonella typhimurium strains TA98, TA100, TA1535, and TA1537 were exposed (in the presence and absence of activation) for 48 hours in triplicate to concentrations of 0 (DMSO), 25, 75, 225, 675, and 2025 µg/0.1 ml/plate. **Mutagenicity is not indicated**. **Unacceptable** and not upgradeable (dosing rationale with no evidence of cytotoxicity or precipitation reported, missing results).
(J. Remsen, 5/28/85; upgraded to electronic format, H. Green, 11/2/95).

**254 115258, "Salmonella/Mammalian-Microsome Mutagenicity Test", (E. Deparade, Ciba-Geigy Limited, Basle, Switzerland, Experimental Pathology Laboratories: R-1066.210-222, Report # 851007, 18 November 1985). The test article is identified as CGA 48 988 (metalaxyl) technical with 95.7% purity. Salmonella typhimurium strains TA98, TA100, TA102, TA1535, and TA1537 were exposed in triplicate to concentrations of 0, 20, 78, 313, 1250, and 5000 µg/0.1 ml for 48

hours in the presence and absence of activation. **No increase in reversion frequency. Acceptable.** (H. Green and Gee, 2/9/96)

046, 254 990437, 115259, "L5178Y/TK$^{+/-}$ Mouse Lymphoma Mutagenicity Test", (F.F. Strasser, Ciba-Geigy Limited, Basle, Switzerland, Report # 811258, 1 February 1982 and supplement dated 14 November 1985). The test article is identified as CGA 48 988 (metalaxyl) technical with 94.1% purity. L5178Y/TK$^{+/-}$ mouse lymphoma cells were exposed for 4 hours with eight replicates to concentrations of untreated, 0, 0.125, 0.25, 0.50, and 1.0 mg/ml without activation and to untreated, 0, 0.0625, 0.125, 0.25, and 0.50 mg/ml with activation. **No increase in mutation frequency.**. **Unacceptable** and not upgradeable (no dosing rationale, no repeat assay). (J. Remsen (Gee), 5/31/85; H. Green and Gee, 2/9/96).

CHROMOSOME EFFECTS

046 990433, "Test for Non-Disjunction on Saccharomyces Cerevisiae D 61 with CGA 48988 (Test for Mutagenic Properties in Yeast Cells)", (Dr. P. Arni, Ciba-Geigy Limited, Protection of Health and Environment, Toxicology, Basle, Switzerland, Report # 79/1891, 10 April 1980). The test article is identified as CGA 48988 (metalaxyl). Saccharomyces cerevisiae D 61 cells were exposed (5 plates per group) without activation to 0 (DMSO), 40, 200, and 1000 µg/ml for 16 hours. **Mutagenicity is not indicated**. **Unacceptable**, not upgradeable (no activation, dosing level justification). (J. Remsen, 5/30/85; updated to electronic format, H. Green, 11/9/95).

046 990436, "Nucleus Anomaly Test in Somatic Interphase Nuclei, CGA 48988, Chinese Hamster (Test for Mutagenic Effects on Bone Marrow Cells)", (Dr. M. Langauer and Prof. Dr. D. Muller, Ciba-Geigy Limited, Protection of Health and Environment, Toxicology, Basle, Switzerland, Report # 78-3007, 18 June 1979). The test article is identified as CGA 48988 (metalaxyl) technical with 98% purity. 6 Chinese hamsters per sex per group were treated twice on consecutive days by gavage at 0, 595, 1190, and 2380 mg/kg/day. Bone marrow was sampled 24 hours after the second dosing. **Mutagenicity is not indicated**. **Unacceptable**, not upgradeable (dosing level rationale inadequate, sampling times, species used not justified). (J. Remsen, 5/31/85; updated to electronic format, H. Green, 11/6/95).

**** 254 115265**, "Clastogenic Evaluation of Metalaxyl Technical, CGA-48988 Tech., in an In Vitro Cytogenetic Assay Measuring Chromosomal Aberration Frequencies in Chinese Hamster Ovary (CHO) Cells", (James L. Ivett, Hazleton Biotechnologies, Kensington, MD., Report # 8584, March 1986). The test article is identified as metalaxyl technical (CGA-48988 technical, 95.7%)
Chinese hamster ovary cells (CHO-WBL) were exposed in duplicate (except controls), in the presence and absence of activation (Aroclor 1254 induced male rat liver S9 fraction), to concentrations of untreated medium, solvent control (DMSO), 150, 300, 900, and 1200 µg/ml for 2 hours (activated) and 17.6 hours (non-activated). **An increased frequency of chromosomal aberrations is indicated under non-activated conditions at the highest concentration only**. **Acceptable** (H. Green and Gee, 2/9/96)

003, 254 990440, 115266 "Dominant Lethal Study - CGA 48988 Technical, Mouse (Test for Cytotoxic or Mutagenic Effects on Male Germinal Cells) and Supplement", (Dr. H. Fritz, Ciba-Geigy Limited, Basle, Switzerland, Pharmaceuticals Division, Toxicology/Pathology, Report # 327761, 23 February 1978 and Supplement dated 7 November 1985). The test article is identified as CGA 48988 (metalaxyl, batch P3) technical. 20 NMRI-derived male mice per group received a single oral dose of 0 (CMC), 65, and 195 mg/kg. Beginning immediately after treatment, each male was placed with 2 untreated females per week for 8 weeks. No conclusive evidence of a dominant lethal affect up to 195 mg/kg (1/3 the oral LD50) **Unacceptable** and not upgradeable (inadequate dosing level, no positive control). (J. Remsen, 5/28/85; H. Green and Gee, 2/9/96).

DNA DAMAGE

046 990434, "Saccharomyces cerevisiae D7/Mammalian-Microsome Mutagenicity Test In Vitro with CGA 48988 (Test for Mutagenic Properties in Yeast Cells)", (Dr. P. Arni, Ciba-Geigy Limited, Protection of Health and Environment, Toxicology, Basle, Switzerland, Report # 811561, 18 January 1982). The test article is identified as CGA 48988 (metalaxyl). Saccharomyces cerevisiae D7 cells were exposed (10 plates per group) in the presence (6 hours) and absence (2 hours) of activation to 0 (DMSO), 2000, 4000, and 8000 µg/ml. **Mutagenicity is not**

indicated. **Unacceptable** and not upgradeable (dosing level justification, individual plate counts, test material characterization, borderline activity with the positive control). (J. Remsen, 5/30/85; updated to electronic format, H. Green, 11/8/95).

046 990435, "Mutagenicity Test on Saccharomyces Cerevisiae MP-1 in Vitro with CGA 48988 (Test for Mutagenic Properties in Yeast Cells)", (Dr. P. Arni, Ciba-Geigy Limited, Protection of Health and Environment, Toxicology, Basle, Switzerland, Report # 79/1346, 10 April 1980). The test article is identified as CGA 48988 (metalaxyl). Saccharomyces cerevisiae MP-1 cells were exposed (10 plates/dose level) to 0 (DMSO), 40, 200, and 1000 µg/ml for 3.5 hours in the absence of activation. **Mutagenicity is not indicated**. **Unacceptable** and not upgradeable (no activation, no dosing level rationale). (J. Remsen, 5/30/85; updated to electronic format, H. Green, 11/7/95).

046, 254 990439, 115260, "Autoradiographic DNA Repair Test on Rat Hepatocytes, CGA 48988, (In Vitro test for DNA-Damaging Properties) and Supplement", (Dr. E. Puri, Ciba-Geigy Limited, Basle, Switzerland, Report # 811259, 19 January 1982 and Supplement dated 18 November 1985). The test material is identified as CGA 48988 (metalaxyl) technical with 94.1% purity. Hepatocytes from male Tif: RAI f (SPF) rats were exposed in quadruplicate to untreated medium, 0 (DMSO), 16, 80, 400, and 2000 µg/ml for 5 hours. **No increase in unscheduled DNA synthesis. Acceptable. (J. Remsen, 5/31/85; H. Green and Gee, 2/9/96).

254 115261, "Autoradiographic DNA Repair Test on Rat Hepatocytes", (Dr. E. Puri, Ciba-Geigy Limited, Basle, Switzerland, Experimental Pathology, Report # 851004, 25 November 1985). The test article is identified as CGA 48 988 (metalaxyl) technical with 95.7% purity. Hepatocytes from male Tif: RAIf(SPF) rats were exposed in quadruplicate to 0 (DMSO), untreated medium, 16, 80, 400, 2000 µg/ml for 5 hours. **No increase in unscheduled DNA synthesis. Acceptable. (H. Green and Gee, 2/9/96).

NEUROTOXICITY

Not required at this time.